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(54) Title: STABLE CLEAR SOLUTIONS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR INCORPORATION INTO GELATIN CAPSULES

(57) Abstract

This invention comprises chemically and physically stable, clear solutions of non-steroidal anti-inflammatory drugs dissolved in dimethylisosorbide or mixtures of dimethylisosorbide with food stuff oils, propylene glycol, polysorbate, polyethelene glycol or other commonly used carriers or solvents which may be encased in soft gelatin capsule shells.

Combination

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STABLE CLEAR SOLUTIONS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR INCORPORATION INTO GELATIN CAPSULES

Field of the Invention

This invention relates to the field of pharmaceutical drug compositions comprising combinations of dimethylisosorbide and non-steroidal anti-inflammatory drugs.

Information Disclosure

U.S. Patent 4,228,162, issued October 14, 1980, Louis A. Luzzi, *et al.*, *Dimethyl Isosorbide in Liquid Formulation of Aspirin.*

U.S. Patent 4,927,638, issued May 22, 1990, G. Bykadi, *et al.*, *Etoposide Solutions.*

U.S. Patent 4,859,709, issued August 22, 1989, David A. Rawlins, *Pharmaceutical Composition.*

U.S. Patent 3,699,230, issued October 17, 1972, Robert O. Beauchamp, Jr. *et al.*, *Dimethylisosorbide Solvent for Muscle Relaxant Drugs.*

E.P. 0 650 721 A1, published 03.05.95 Bulletin 95/18, applicant Hanmi Pharm. Ind. co., Ltd., inventor, Woo, Jong Soo, *Cyclosporin Soft Capsule.*

U.S. Patent 5,468,502, issued November 21, 1995, Andrew A. Argiriadi, et al., *Ibuprofen Enhancing Solvent System.*

Background

It is increasingly important in today's market place to provide medications that are pleasing to the consumer. The size, shape and overall appearance of a medicament can play an important role in the acceptance of the medicine by the public.

Clear solutions of drugs incorporated into soft gelatin capsules have become an increasingly important segment of the over-the-counter drug market. Now the authors report herein the development of gelatin capsules filled with clear stable solutions of non-steroidal anti-inflammatory drugs.

Dimethylisosorbide, or DMI, is totally water miscible and studies have shown it is practically nontoxic in low doses. The highly water soluble nature of DMI makes it an unlikely choice as a fill material for gelatin capsules.

DMI, has been used as a solvent to produce liquid solutions of aspirin, see U.S. Patent 4, 228,162, tetracyclines, see U.S. Patent 3,219,529, muscle relaxants, see U.S. Patent 3,699,230, and steroids, see U.S. Patent 4,082,881; however it is only

rarely chosen as a carrier for filling soft gelatin capsules.

DMI has been suggested as a material to fill gelatin capsules where it is combined with etoposide, a drug used for the treatment of refractory testicular cancer and small cell lung cancer. Etoposide is currently being marketed under the tradename VePesid ®, however, the suggested dimethylisosorbide containing formula is not known to be marketed. See U.S. Patent 4,927,638. Etoposide is extremely soluble in a DMI. There is also a suggestion of using DMI as part of a microemulsion solution used to fill soft gelatin capsules. See E.P. 0 650 721 A1.

Non-steroidal anti-inflammatory drugs such as ibuprofen, flurbiprofen, and naproxen as free acids are relatively insoluble in water and in many of the typical oil carriers used in soft gelatin capsules. Suspensions of these drugs in oil are possible for filling into soft gelatin capsules; however, as mentioned earlier these are not preferred by the consumer.

Summary of the Invention

Soft gelatin capsules containing a composition comprising clear stable solutions of dimethylisosorbide (DMI) and an nsaid. Soft gelatin capsules containing a composition comprising clear stable solutions of dimethylisosorbide and optionally comprising carrier oils. Soft gelatin capsules where the compositions contained by the soft gelatin capsules comprise at least 40 percent dimethylisosorbide or the compositions may comprise up to 35 percent propylene glycol, up to 60 percent polysorbate, or up to 60 percent polyethylene glycol. The soft gelatin capsules may contain compositions comprising about 30, 25, 20, 15, 10, 5 or 0 percent propylene glycol, more preferred is up to 50 percent polysorbate, or up to 50 percent polyethylene glycol. The nsaid may be selected from: propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, or oxicams and their derivatives. The polysorbate may be polysorbate 80, the polyethylene glycol may be polyethylene glycol 400. The nsaid is a compound or compounds selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, or oxicams and their derivatives. The propionic acid derivative may be a compound or compounds selected from ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen, and fluprofen and their derivatives or their pharmaceutically acceptable salts, esters or derivatives. The acetic acid derivative may be a compound or compounds selected from sulindac, indomethacin and their salts or derivatives, or a salt such as tolmetin

sodium. The fenamic acid derivative may be selected from mefenamic acid and its salts or derivatives, or a salt such as meclofenamate sodium. The biphenylcarboxylic acid derivatives may be selected from difunisal and flufenisal and their salts and derivatives. The oxicam may be selected from oxicam, piroxicam, sudoxicam, and isoxicam and their salts and derivatives. These compositions make pharmaceutically elegant solutions that are particularly suitable for filing soft gelatin capsules.

Additional Description of the Invention and Description of the Preferred Embodiment(s)

Definitions

DMI is dimethylisosorbide.

Soft gelatin capsules are any type of gelatin capsule suitable for filling with liquid solutions. These capsules may be referred to with other names such as soft elastic capsules, soft gelatin, soft gel, soft liquid gel, sometimes makers of these products use trademark names such as, Liquid Gel ®, Liquid Caps ®, DOXIDAN ® etc.

There are many non-steroidal compounds or agents which have anti-inflammatory effects. In the current invention the non-steroidal anti-inflammatory to be combined in a pharmaceutically acceptable composition with DMI is selected from one of the following categories:

Propionic acid derivatives
Acetic acid derivatives
Fenamic acid derivatives
Biphenylcarboxylic acid
Oxicams.

The term "NSAID" or "nsaid" used herein is intended to mean any non-steroidal anti-inflammatory compound, including the salts and esters thereof, falling within one of the five structural categories above, but excluding acetaminophen and phenacetin. The specific compounds falling within the foregoing definition of non-steroidal anti-inflammatory drugs for use in the present invention are known to those skilled in the art.

Of the propionic acid derivatives for use herein, ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen, and fluprofen are particularly preferred compounds. Preferred acetic acid derivatives include tolmetin sodium, sulindac, and indomethacin. Preferred fenamic acid derivatives include mefenamic

acid and meclofenamate sodium. Preferred biphenylcarboxylic acid derivatives include difunisal and flufenisal. Preferred oxicams include oxicam, piroxicam, sudoxicam, and isoxicam.

Also included are derivatives of these compounds, their salts, esters and derivatives. These salts may also be considered "pharmaceutically acceptable salts" and this refers to the relatively non-toxic, inorganic and organic acid addition salts and esters and, where the compounds of this invention also contain an acidic functional group, the alkali and alkaline earth metal salts. These salts can be prepared by reacting the purified compound in its free acid form with a suitable organic or inorganic base and isolating the salt thus formed. Representative alkali or alkaline earth salts include the sodium, potassium, calcium, and magnesium salts and the like. Representative salts formed from reaction with organic bases include but are not limited to those such as formed with arginine, lysine and the like. These salts are readily prepared by methods known in the art. The salts may produce compounds that are more water soluble than the free acids. Additionally, the compounds of this invention may be mixed with DMI in a suitable hydrated form.

There are numerous chemical terms used in this document, terms such as polysorbate, polyethylene glycol, polypropylene glycol, that are frequently given other names. As used herein, these terms should be defined in accordance with the CTFA Cosmetic Ingredient Dictionary, third edition, editors, Estrin, Crosley & Haynes, published by The Cosmetic, Toiletry and Fragrance Association, Inc., 1110 Vermont Ave. N.W., Washington, D.C. 20005, copyright 1973, 1977, 1982. Terms not adequately defined in that publication may be further defined in the Encyclopedia of Conditioning Rinse Ingredients by Anthony L.L. Hunting, Micelle Press, Cranford, New Jersey and London, England, copyright 1987. In accordance with these references, numerical terms used in association with sorbitan derivatives, such as the number "20," have no special or intrinsic significance. As used herein these numbers are referred to being "designated as" or as designations. Numeric terms used in connection with these terms should be interpreted broadly and include all commercially available versions of the products. The word "about" should be interpreted broadly when used in connection with any term.

It is possible that some ingredients herein will form "pharmaceutically acceptable esters" when reacted with various alcohols. Representative esters include but are not limited to those of methyl and ethyl alcohol as well as other alcohols which would be apparent to one skilled in the art. These esters are readily

prepared by methods known in the art. The esters thus produced may form compounds that are more water soluble than the free acids. Additionally, the compounds of this invention may be mixed with DMI in a suitable hydrated form.

A clear solution of the drugs and types of drugs described by this disclosure and used to fill a soft gelatin capsule offer significant commercial advantages. These compositions make pharmaceutically elegant solutions that are particularly suitable for filing soft gelatin capsules. The capsules made with these solutions are also particularly pharmaceutically elegant. Surprisingly and unexpectedly it has been found that the compositions containing at least 40 percent DMI, as described herein, produce a liquid that makes a pharmaceutically elegant fill for gelatin capsules. These clear soft gelatin capsule compatible solutions are not easily obtained using other solvents, carriers, solutions or mixtures.

Although these drugs are relatively insoluble, they are ionizable and chemically reactive in aqueous media and therefore subject to transformation into esters or salts if not formulated properly. In a formulation it is possible the products which may form may be considered as new chemical entities (for regulatory purposes) or it is possible they may be classified as degradation products. In either case, this deviation from the original pure compound is most often undesirable. The authors herein report solutions of the drugs which are not only compatible with soft gelatin capsules but which also prevent the degradation or reactions to form undesirable products.

In clinical practice, the compositions described herein will normally be administered orally, however; the gelatin capsules could also be administered rectally, in the form of pharmaceutical preparations comprising the active ingredient typically in the free acid form but possibly as a pharmaceutically acceptable non-toxic, addition salt, or ester such as the types listed above in association with a pharmaceutically acceptable carrier. The use and administration to a patient to be treated in the clinic would be readily apparent to a physician or pharmacist of ordinary skill in the art.

Compositions and Administrations

The present invention describes how dimethylisosorbide (DMI) can be combined with non-steroidal anti-inflammatory drugs, such as aspirin, ibuprofen, flurbiprofen, and other common compatible carriers, or solvents, such as foodstock oils, oils and solvents such as soybean oil, cottonseed oil, peanut oil, corn oil, safflower oil, canola oil, olive oil, macadamia nut oil, polyethylene glycol, or

polysorbate to produce a clear, aesthetically pleasing liquid filled gelatin capsule. A foodstock type carrier oil is a nontoxic oil, it may be derived from a natural product such as soybean oil, cottonseed oil, peanut oil, corn oil, safflower oil, canola oil, olive oil, macadamia nut oil, or a similar synthetic substitutes, and the like.

Particularly appropriate compatible carriers or solvents are; the oils, propylene glycol, polysorbate and polyethylene glycol. Of the latter, polysorbate 80, (one commercial version is named Tween ® 80) and polyethylene glycol 400 are especially suitable for forming clear stable solutions with the nsaids.

Solutions where the DMI concentration is at least 40 percent appear suitable, although if propylene glycol is used in the composition it cannot comprise more than 35 percent of the contents of the capsule. Soft gelatin capsules containing a composition comprising clear stable solutions of both dimethylisosorbide and an nsaid, selected from but not limited to propionic acid or derivatives, acetic acid or derivatives, fenamic acid or derivatives, biphenylcarboxylic acid or derivatives, or oxicams and their derivatives with or without a compatible carrier or solvent, such as food stock oils, or their pharmaceutically acceptable salts, esters and oils, can be used.

If polysorbate is used with the DMI the polysorbate can be of any designation, such as polysorbates 20, 40, 60, 65, 80 or 85. Polysorbate 80 works well. If the liquid composition contains polyethylene glycol, it should not be of a higher weight than what causes precipitation. Our investigations suggest one upper weight limit of polyethylene glycol is around 900, unless heating and cooling techniques are used. A weight of about 600 to 650 could be used. Polyethylene weights that cause appreciable precipitation in a short period of time would be unacceptable. If propylene glycol is used, its concentration should be less than about 35 percent, concentrations of 40 percent and higher appear to cause capsule deformities, thus diminishing the elegance of the soft gelatin capsule. Liquid solution compositions containing 30 percent propylene glycol were suitable and solutions containing about 25, 20, 15, 10, 5 or 1 percent propylene glycol mixed with the DMI should all be suitable. Food stuff oils are traditional gelatin capsule fill materials and they can also be used with DMI. Their use would only be limited to the extent that they caused precipitation of the drug or otherwise interfered with the elegant appearance of the soft gelatin capsule. Oil concentrations of about 60, 40, 30, 20, 10, or 5 percent should all be suitable. Various combinations of the above may also be suitable.

Various carriers, additives and other oils could be added to these solutions and compositions containing DMI. The carriers, additives and oils can be mixed or combined in various combinations and other drugs, such as pseuodophrine, could also be added to the compositions, provided they do not cause significant precipitation or capsule deformation.

Ibuprofen has been found to be soluble at room temperature in dimethylisosorbide to the extent of 58 grams/100 ml. Flurbiprofen is soluble in dimethylisosorbide at room temperature to the extent of 45 grams/100 ml.

Therapeutic doses of 200 mg ibuprofen or 50 mg of flurbiprofen are appropriate for delivery from a soft gelatin capsule. Should dimethylisosorbide be used as the sole solvent delivering the drug to fill the soft gelatin capsule, a capsule as small as a #2 round or # 2 oval soft gel can be used for 50 mg of flurbiprofen while a # 6 round, # 7½ oval, or # 6 oblong can be used to deliver 200 mg of ibuprofen.

If one needed to incorporate this quantity of drug in 0.986ml to fill a #16 oval soft gelatin capsule, it would be necessary to utilize a carrier in addition to DMI. The 200 mg of ibuprofen per capsule translates to 10.2 grams per 50 ml of fill while the 50 mg dose of flurbiprofen would require 2.55 grams of drug per 50 ml of fill. Based on the solubility of these drugs, there is sufficient capsule volume to dissolve them in DMI.

Using skills available to one ordinarily skilled in the art and using standard texts and procedures pharmaceutically suitable mixtures of dimethylisosorbide and drug are combined with a carrier if needed and this solution is used to prepare soft gelatin capsules.

Using the information above, one ordinarily skilled in the art could practice this invention. An expert in pharmaceutical compositions could easily optimize this invention. The following examples are intended to illustrate and not limit the invention.

Various blends of dimethylisosorbide with commonly used soft gelatin capsule fillers were prepared and drug dissolved in them. The various blends could be used to fill soft gelatin capsules.

Various embodiments of the invention are described below, the embodiments shown are intended to illustrate the invention and not limit it in any manner.

Examples 1. Approximately 50/50 or 40/60 blends of dimethylisosorbide and: corn

oil, cottonseed oil, soybean oil, or propylene glycol were prepared and 10.2 grams of ibuprofen dissolved in 50 ml of each blend.

Examples 2. Approximately 60/40, 80/20, 90/10 blends of dimethylisosorbide and propylene glycol were prepared and 10.2 grams of ibuprofen dissolved in 50 ml of each blend.

Examples 3. Approximately 80/20, 90/10, 70/30 blends of dimethylisosorbide and: propylene glycol were prepared and 2.55 grams of flurbiprofen dissolved in 50 ml of each blend.

Examples 4. Approximately 50/50 blends of either dimethylisosorbide and polysorbate 80 (Tween 80) or dimethylisosorbide and polyethylene glycol (including peg 400) containing no drug, 10.2 grams/50 ml of ibuprofen or 2.55 grams/50ml of flurbiprofen were prepared.

Examples 5. Approximately 100 percent DMI solutions were prepared.

Dimethylisosorbide compatibility with soft gelatin capsules was demonstrated by immersing intact DOXIDAN® capsules in dimethylisosorbide either alone or in combination as blends, as described above. All gelatin capsules remained intact except those where drug was combined with 60/40 or 50/50 blend of propylene glycol and dimethylisosorbide.

The solutions of ibuprofen and flurbiprofen with DMI either alone or in various combinations with other excipients remained clear and the drugs are chemically unaltered. Gelatin capsules exhibit no appreciable deterioration after exposure to the solutions.

Claims

1. Soft gelatin capsules containing a composition comprising clear stable solutions of both dimethylisosorbide and an nsaid, or combinations thereof, selected from but not limited to, propionic acid or derivatives, acetic acid or derivatives, fenamic acid or derivatives, biphenylcarboxylic acid or derivatives, or oxicams and their derivatives with or without a compatible carrier or solvent, or combinations thereof, such as food stock oils, polysorbates, polyethylene glycols, propylene glycol, or combinations thereof, or their pharmaceutically acceptable salts, esters and oils, with the proviso that if propylene glycol is used in the composition it cannot comprise more than 35 percent of the contents of the capsule and if the composition contains polyethylene glycol, it is not of a higher weight polyethylene glycol than those weights that are liquids at room temperature.

2. Soft gelatin capsules of claim 1 where the compositions contained by the soft gelatin capsules comprise at least 40 percent dimethylisosorbide.

3. Soft gelatin capsules of claim 2 where the compositions comprise up to 35 percent propylene glycol, or up to 60 percent: polysorbate, polyethylene glycol or food stock oils.

4. Soft gelatin capsules of claim 2 where the compositions comprise up to 30 percent propylene glycol, up to 50 percent polysorbate, or up to 50 percent polyethylene glycol.

5 . Soft gelatin capsules of claims 3 or 4 where the polysorbate is a polysorbate of about 20, 40, 60, 65, 80 or 85 designation.

6. Soft gelatin capsules of claims 3 to 5 where the polysorbate is a polysorbate designated as 80.

7. Soft gelatin capsules of claim 3 where the polyethylene glycol is a polyethylene glycol of about or less than about 600 weight.

8. Soft gelatin capsules of claims 3 or 7 where the polyethylene glycol is a polyethylene glycol of about 400 weight.

9. Soft gelatin capsules of claim 3 where the propylene glycol concentration is from about 1 to about 25 percent of the composition contained by the soft gelatin capsule.

10. Soft gelatin capsules of claim 9 where the propylene glycol concentration is from about 1 to about 10 percent of the composition contained by the soft gelatin capsule.

11. A soft gelatin capsule of claim 10 where there is essentially no propylene glycol.

12. A soft gelatin capsule of claims 1 to 11 where the food stock oil is selected from canola, safflower, cottonseed, soybean, peanut, corn, olive, or macadamia nut, oils.

13. A soft gelatin capsule of claims 1 to 12 where the oil is selected from corn, soybean, canola or safflower oil.

14. A soft gelatin capsule of claim 13 where the oil is selected from corn oil.

15. A soft gelatin capsule of claims 1 to 14 where the nsaid is a compound or compounds selected from propionic acid or derivatives, acetic acid or derivatives, fenamic acid or derivatives, biphenylcarboxylic acid or derivatives, or oxicams and their derivatives.

16. Soft gelatin capsules of claim 15 where the nsaid is selected from propionic acid or derivatives.

17. A soft gelatin capsule of claims 1 to 16 where the propionic acid or derivative is a compound or compounds selected from ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen, and fluprofen and their salts or derivatives.

18. Soft gelatin capsules of claim 17 where the propionic acid or derivative is selected from ibuprofen, naproxen or flurbiprofen or their derivatives.

19. Soft gelatin capsules of claim 18 where the propionic acid derivative is ibuprofen or its derivative.

20. Soft gelatin capsules of claim 18 where the propionic acid derivative is naproxen or its derivative.

21. Soft gelatin capsules of claim 18 where the propionic acid derivative is flurbiprofen or its derivative.

22. Soft gelatin capsules of claim 5 where the propionic acid derivative is selected from ibuprofen, naproxen or flurbiprofen or their derivatives.

23. Soft gelatin capsules of claim 22 where the polysorbate is designated as 80.

24. Soft gelatin capsules of claim 23 where the propionic acid derivative is ibuprofen or its derivative.

25. Soft gelatin capsules of claim 7 where the propionic acid derivative is selected from ibuprofen, naproxen or flurbiprofen or their derivatives.

26. Soft gelatin capsules of claim 25 where the polyethylene glycol is about 400 weight.

27. Soft gelatin capsules of claim 26 where the propionic acid is ibuprofen or its derivative.

28. Soft gelatin capsules of claim 9 where the propionic acid is selected from ibuprofen, naproxen or flurbiprofen or their derivatives.

29. Soft gelatin capsules of claim 28 where the propylene glycol is about 10 percent.

30. Soft gelatin capsules of claim 29 where the propionic acid is ibuprofen or its derivative.

31. Soft gelatin capsules of claim 13 where the propionic acid is selected from ibuprofen, naproxen or flurbiprofen or their derivatives.

32. Soft gelatin capsules of claim 14 where the propionic acid is ibuprofen or its derivatives.

33. A soft gelatin capsule of claim 15 where the nsaid is a compound or compounds selected from acetic acid or its derivatives.

34. A soft gelatin capsule of claim 33 where the acetic acid derivative is a compound or compounds selected from sulindac, and indomethacin and their salts or derivatives or the salt tolmetin sodium and its derivatives.

35. A soft gelatin capsule of claim 15 where the nsaid is a compound or compounds selected from fenamic acid or its derivatives.

36. A soft gelatin capsule of claim 35 where the fenamic acid derivative is selected from mefenamic acid and its salts or derivatives or meclofenamate sodium and its derivatives.

37. A soft gelatin capsule of claim 15 where the nsaid is a compound or compounds selected from biphenylcarboxylic acid derivatives.

38. A soft gelatin capsule of claim 37 where the biphenylcarboxylic acid derivatives are selected from difunisal and flufenisal and their salts and derivatives.

39. A soft gelatin capsule of claim 15 where the nsaid is a compound or compounds selected from oxicams and their derivatives.

40. A soft gelatin capsule of claim 39 where the oxicam is selected from oxicam, piroxicam, sudoxicam, and isoxicam and their salts and derivatives.

41. A soft gelatin capsule substantially as herein described.

INTERNATIONAL SEARCH REPORT

Inte tional application No.
PCT/US 96/10687

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/48, A61K 47/26, A61K 31/19, A61K 31/40, A61K 31/54
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, WPIL, CLAIMS, EMBASE, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A1, 9200725 (FARCON AG), 23 January 1992 (23.01.92), the claims ---	1-41
Y	US, A, 4228162 (LOUIS A. LUZZI ET AL), 14 October 1980 (14.10.80), column 4, line 67 - column 5, line 52, claims ---	1-41
Y	EP, A1, 0359184 (BRISTOL-MYERS COMPANY), 21 March 1990 (21.03.90), page 3, line 26 - line 38, claims --- --------	1-41

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 Sept 1996	15. 11. 96
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer ANNELI JÖNSSON Telephone No.

SA 37027

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/96

International application No.
PCT/US 96/10687

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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